REMARKS AND ARGUMENTS

I. The Information Disclosure Statement

At page 2 of the office action, the Examiner states that some of the references listed on the Information Disclosure Statement were not considered because parent application 07/971,857 in which the references were submitted is not available to the Examiner. The Examiner has provided a copy of Applicants' information disclosure statement in which the Examiner marked references that were not considered.

To facilitate the examination of the above-identified patent application, Applicants submit herewith copies of the references that the Examiner could not obtain from the parent application.

II. Patentability Arguments

A. The Claim Rejections Under 35 USC §102(e) Should Be Withdrawn

At page 4 of the Office action, the Examiner maintained the rejection of claims 1-5, allegedly as being anticipated by *Ladner et al.* U.S. Patent 5,223,409 (*Ladner et al.*). The Examiner alleges that *Ladner et al.* anticipate the instant claim 1 because it teaches methods of displaying binding proteins on the surface of filamentous bacteriophage via nucleic acid sequences including gIII and screening for target molecule binding wherein phagemids and helper phage may be utilized pointing to the abstract; columns 1, 4-12, 15-105, Examples I-XVI; and claims 1-66 of *Ladner et al.*

The Examiner also alleges that *Ladner et al.* anticipate claim 2 because it teaches separating bacteriophage expressing binding proteins from the target molecules in columns 10-12, and 93-98.

The Examiner alleges that *Ladner et al.* anticipate claim 3 because it teaches recovering of separated bacteriophage in columns 10-12, 98-99.

The Examiner alleges that *Ladner et al.* anticipate claim 4 because Ladner et al. teach expressing the binding protein in another expression system including bacterial spores, and artificial methods, etc. in columns 8, 10, 50-77.

Finally, with respect to claim 5, the Examiner alleges that *Ladner et al.* teach utilizing the methods to express antibodies including the Fc portion in columns 15-16.

The Applicants respectfully traverse the rejections in view of the foregoing amendments and the following comments which distinguish the phagemids of *Ladner et al.* with those presently claimed.

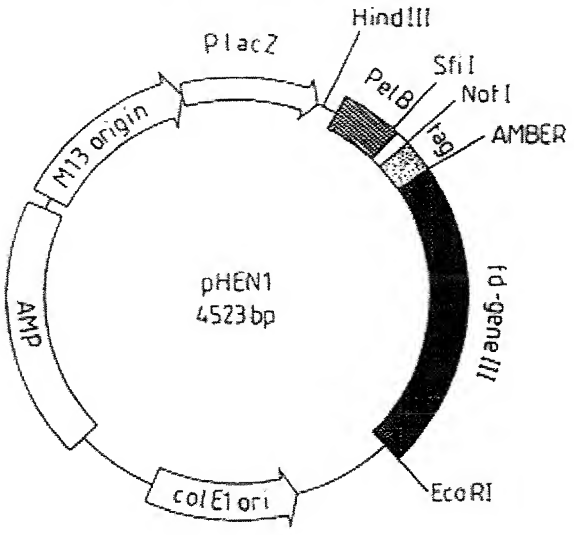
The claims as presently amended include the recitation that the only nucleotide sequences in the phagemid that are derived from filamentous bacteriophage are an origin of replication and a nucleotide sequence encoding a gene III capsid protein.

Support for this amendment can be found throughout the specification as filed. For example, paragraph [0020] of the published specification provides:

> "In all embodiments where the present applicants have used phagemids, they have used a helper phage and **the only sequences derived from filamentous bacteriophage in the phagemids are the origin of replication and gene III sequences**." (emphasis added)

The Examiner is further referred to Example 24 of the specification which concerns the construction of the phagemid pHEN1 derived from pUC119. pHEN1 has the features shown in FIG. 26 which exemplifies phagemids according to the present invention.

Fig.26(a).



Because phagemids of the present invention are those in which the only filamentous bacteriophage derived nucleotide sequences are an origin of replication and a nucleotide sequence encoding a gene III protein, they differ significantly from those described in *Ladner et al.* who teach against the use of phagemids lacking a full phage genome.

The Examiner cited several passages from *Ladner et al.* in support of the rejection of the pending claims. However, the referenced sections help illustrate the distinction between the phagemids of *Ladner et al.* and those presently claimed. One of the cited passages (column 76, lines 55-67) specifically states:

> "Phage prepared from these cells would be designated XY24. Phagemids such as Bluescript K/S (sold by Stratagene) are not preferred for our purposes because Bluescript does not contain the full genome of M13 and must be rescued by coinfection with competent wild-type M13. **Such coinfections** could lead to genetic recombination yielding heterogeneous phage **unsuitable for the purposes of the present invention.** Phagemids may be entirely suitable for developing a gene that causes an IPBD to appear on the surface of phage-like genetic packages." (emphasis added)

The description of construction of phagemid vectors in Example 1 at the lines identified by the Examiner (as below) makes it clear that the phagemid vector used in the cited reference is in fact precisely of the kind that column 76 quoted above says should be used to prevent recombination, i.e. phagemids containing the full phage genome. The pGEM vectors, containing the features identified at column 106, lines 34-39, are used to assemble different gene constructs that are combined into vectors containing all of the genes of M13. See e.g. column 106, lines 54-58. The following disclosure in Ladner et al is also of relevance for the present consideration as to how Ladner et. al methods differ from those recited by the pending claims.

Column 106, lines 5-10:

> A. Operative cloning vectors (OCV)
> The operative cloning vectors are M13 and phagemids derived from M13 or f1. The initial construction was in the f1-based phagemid pGEM-3Zf(-)^{TM}. (Promega Corp., Madison, Wis.).

Lines 34-39:

> OCV based upon pGEM-3Zf
> pGEM-3Zf.TM. (Promega Corp., Madison, Wis.) is a plasmid-based vector containing the amp gene, bacterial origin of replication, bacteriophage fl origin of replication, a lacZ operon containing a multiple cloning site sequence, and the T7 and SP6 polymerase binding sequences.

Lines 54-58:

> ii) OCV based upon M13mp18
> M13mp18 (YANI85) is an M13 bacteriophage-based vector (available from, inter alia, New England Biolabs, Beverly, Mass.) consisting of **the whole of the phage genome** into which has been

> inserted a lacZ operon containing a multiple cloning site sequence (MESS77). Two restriction enzyme sites were introduced into M13mp18 using standard methods. A BamHI recognition site (GGATCC) was introduced at the 5' end of the lacZ operon by the mutation of bases C_{6003} and G_{6004} to A and T respectively (numbering of Messing). This mutation also destroyed a unique NarI site. A SalI recognition site (GTCGAC) was introduced at the 3' end of the operon by the mutation of bases A_{6430} and C_{6432} to C and A respectively. A construct combining these variants of M13mp18 was designated M13-MB1/2. (emphasis added)

Column 111, lines 15-40:

> c) M13-gene-III-signal::bpti::mature-VIII-coat-protein
>
> We may also construct, as depicted in FIG. 5, M13-MB51 which would carry a gene encoding a fusion of M13-gene-III-signal-peptide to the previously described BPTI::mature VIII coat protein. First the BstEII site that follows the stop codons of the synthetic gene VIII is changed to an AlwNI site as follows. DNA of pGEM-MB26 is cut with BstEII and the ends filled in by use of Klenow enzyme; a blunt AlwNI linker is ligated to this DNA. This construction is called pGEM-MB26Alw. The XhoI to AlwNI fragment (approximately 300 bp) of pGEM-MB26Alw is purified. RF DNA from phage MK-BPTI (vide infra) is cut with AlwNI and XhoI and the large fragment purified. These two fragments are ligated together; the resulting construction is named M13-MB51. Because M13-MB51 contains no gene III, the phage can not form plaques. M13-MB51 can, however, render cells Km^R Infectious phage particles can be obtained by use of helper phage. As explained below, the gene III signal sequence is capable of directing (BPTI)::(mature-gene-III-protein) to the surface of phage. In M13-MB51, we have inserted DNA encoding gene VIII coat protein (50 amino acids) and three stop codons 5' to the DNA encoding the mature gene III protein.

The above passage, with reference also to Figure 5, is similarly describing the combination of a fragment of a pGEM based vector with a large fragment of MK-BPTI which is explicitly said to be "RF DNA", i.e. Replicative Form DNA which is the mature, full length (double-stranded) phage genome.

Because *Ladner et al.* discloses a method in which phagemids, unlike those of the present invention, comprise the full bacteriophage genome and further states that those which do not contain the full genome are not suitable for their purposes and further when discussing the use of helper phage they do so in the context of providing a gene III protein, the Applicants respectfully

submit that *Ladner et al.* cannot properly anticipate any of the pending claims as a matter of law and, therefore, the rejections of the claims over *Ladner et al.* should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper order for allowance and such allowance is respectfully solicited. The Examiner is hereby respectfully invited to contact the undersigned attorney at the number listed below with any questions, comments or suggestions relating to this application. Should any additional fees be required for further prosecution of the above-identified patent application, the Commissioner is authorized to deduct any such fees from Howrey LLP Deposit Account No. 08-3038, referencing the above-identified docket number.

Respectfully submitted,
HOWREY LLP

By: _____
David W. Clough, Ph.D.
Registration No.: 36,107
Direct Telephone: (312) 595-1408
Customer ID No. 22930

Dated: September 24, 2007
HOWREY LLP
ATTN: Docketing Department
2941 Fairview Park Drive, Suite 200
Falls Church, VA 22042-9922
Telephone No.: (703) 663-3600
Facsimile No.: (212) 383-7195